PEER REVIEW HISTORY

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incorporation of assessments of risk of bias of primary studies in systematic reviews of randomized trials: a cross-sectional review
AUTHORS	Hopewell, Sally; BOUTRON, Isabelle; Altman, Doug; Ravaud, Philippe

VERSION 1 - REVIEW

REVIEWER	Lars G. Hemkens Senior Scientist Basel Institute for Clinical Epidemiology and Biostatistics
REVIEW RETURNED	13-May-2013

GENERAL COMMENTS	In their manuscript „Incorporation of assessments of risk of bias of primary studies in systematic reviews of randomized trials: a cross-sectional review", Hopewell and colleagues raise attention on a major challenge for systematic reviewers. The in my view most important finding is that the assessment of risk of bias of primary studies included in systematic reviews of RCTs rarely has an impact on the quantitative evidence synthesis. Overall, this is a well-written and clearly structured paper. The research question is clearly defined and appropriately answered, the methods are clear and the results appropriately reported and interpreted. I absolutely agree with the author's interpretation and found all conclusions justified. I have not identified any major shortcomings. However, the novelty and (high) relevance of this analysis could be more emphasized, especially with regard to the cited paper by Moja et al. (Ref. 17) which describes a similar analysis on the basis of publications up to 2002. Eight years ago, Moja et al. stated "We believe that more research is needed to understand how best to assess and incorporate the methodological quality of primary studies into the results of systematic reviews". Hopewell and colleagues demonstrated that there was no progress in this regard the last 10 years. This is a striking finding. So despite all the valuable efforts to transparently report and display the potential of bias of primary studies (which is very time-consuming), the impact on the analyses is rarely (formally) assessed e.g. by performing stratified meta-analyses. I would therefore suggest perusing the "What this study adds" section in this regard because I think it was already known that there is a problem - the striking novelty is more the fact that there was nearly no improvement. While I absolutely agree with the statement

	"It is not sufficient to present the analysis and interpretation of a systematic review based on all included studies ignoring flaws identified during the assessment of risk of bias. The higher the proportion of studies assessed at high risk of bias the more cautious authors should be in the analysis and interpretation of the results." - I think this is not really what this study adds since the authors have not directly analyzed the impact of the non-incorporation of the risk of bias, so the statement is more an interpretation than a conclusion supported by the data.

REVIEWER	Alessandro Montedori,MD Regional Health Authority of Umbria, Italy
REVIEW RETURNED	14-May-2013

GENERAL COMMENTS	This paper describes how assessments of risk of bias of RCTs included in systematic reviews are carried out and how such assessments are incorporated into the statistical analysis and overall findings. Importance of work: There is considerable evidence that key information is often poorly reported in systematic reviews (SRs) (Moher 2007); that's why important agencies and international groups have produced guidelines and statements where the task of assessing the risk of bias of individual studies (as a component of assessing the strength of a body of evidence) is essential to improve the conduct and reporting of systematic reviews and meta-analyses. (Higgins 2008; CRD Guidance 2009; Viswanathan 2012; Moher 1999; Moher 2009) I think Authors correctly point out this important issue (assessments of risks of bias) in SRs reporting and how such assessments are included in overall findings. This paper is therefore of potential importance to a general readership, and particularly to systematic reviewers, in order to improve the suboptimal reporting of systematic reviews and meta-analyses. Originality The work is similar and findings consistent with those of Moja 2005 that evaluated SRs published between 1995 and 2002. The present research study underlines that in the last ten years no improvement has been observed in how systematic reviews incorporate the assessment risk of bias of primary studies into formal statistical analysis. Scientific reliability The aim of the study and outcome measures are clearly defined with appropriate reference to the literature. The overall study design is satisfactory. The study sample (Cochrane and non-Cochrane systematic reviews published between 1 January and 31 March 2012) is adequately described. * Methods The planned study sample is clearly defined together with inclusion criteria; methods are adequately described in all aspects: study sample selection, data extraction and data analysis.

	* Results Study findings are well presented. In Tables 1-2-3 are clearly described the outcome measures: characteristics of included SRs; method used for risk of bias assessment in primary studies; presentation and incorporation of risk of bias assessments into the analysis of individual systematic reviews. * Interpretation and conclusions The study aims have been answered. The findings are consistent with other studies (Moher 2007; Jadad 1998). Results show better reporting in Cochrane reviews and specifically the fact that they were much more likely to assess individual methodological component as I expected. I agree with the Authors about the potential underestimation of the problem by extracting non-Cochrane reviews from DARE database compared to systematic reviews identified from other sources. Finally this work points out an important issue: both Cochrane and non-Cochrane reviews largely failed in how risk of bias assessment were incorporated into the statistical analysis and interpretation of the overall conclusions. * References: Updated and relevant. *Abstract/summary/key messages? Information contained are consistent and reflect accurately what the paper says. References Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med 2007;4:e78. Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. [updated February 2008]. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.0.0. The Cochrane Collaboration; 2008.Available: http://www.cochrane-handbook.org/. Accessed 26 May 2009 Centre for Reviews and Dissemination (2009) Core principles and methods for conducting a systematic review of health interventions. Systematic reviews: CRD's guidance for undertaking reviews in health care. York: University of York. pp. 2–99. Available: http://www.york.ac.uk/inst/crd/index_guidance.htm. Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters M, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. 2012 Mar 08. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from http://www.ncbi.nlm.nih.gov/books/NBK91433/ Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, et al. Improving the quality of reports of meta-analyses of randomised controlled

	trials: The QUOROM statement. Quality of Reporting of Metaanalyses. Lancet 1999;354:1896e900. Moher D, Tetzlaff J, Altman DG, for the PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 339: b2535. Moja LP, Telaro E, D'Amico R, Moschetti I, Coe L, Liberati A. Assessment of methodological quality of primary studies by systematic reviews: results of the metaquality cross sectional study. BMJ 2005 May 7;330(7499):1053.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
In their manuscript „Incorporation of assessments of risk of bias of primary studies in systematic reviews of randomized trials: a cross-sectional review", Hopewell and colleagues raise attention on a major challenge for systematic reviewers. The in my view most important finding is that the assessment of risk of bias of primary studies included in systematic reviews of RCTs rarely has an impact on the quantitative evidence synthesis.

Overall, this is a well-written and clearly structured paper. The research question is clearly defined and appropriately answered, the methods are clear and the results appropriately reported and interpreted. I absolutely agree with the author's interpretation and found all conclusions justified. I have not identified any major shortcomings.

However, the novelty and (high) relevance of this analysis could be more emphasized, especially with regard to the cited paper by Moja et al. (Ref. 17) which describes a similar analysis on the basis of publications up to 2002. Eight years ago, Moja et al. stated "We believe that more research is needed to understand how best to assess and incorporate the methodological quality of primary studies into the results of systematic reviews". Hopewell and colleagues demonstrated that there was no progress in this regard the last 10 years. This is a striking finding. So despite all the valuable efforts to transparently report and display the potential of bias of primary studies (which is very time-consuming), the impact on the analyses is rarely (formally) assessed e.g. by performing stratified meta-analyses.

I would therefore suggest perusing the "What this study adds" section in this regard because I think it was already known that there is a problem - the striking novelty is more the fact that there was nearly no improvement. While I absolutely agree with the statement "It is not sufficient to present the analysis and interpretation of a systematic review based on all included studies ignoring flaws identified during the assessment of risk of bias. The higher the proportion of studies assessed at high risk of bias the more cautious authors should be in the analysis and interpretation of the results." - I think this is not really what this study adds since the authors have not directly analyzed the impact of the non-incorporation of the risk of bias, so the statement is more an interpretation than a conclusion supported by the data.

RESPONSE: We agree with these comments regarding the Moja et al paper and have strengthened this section in the discussion. We have also revised the "What this study adds" section and deleted the statement suggested above and added information highlighting the lack of improvement in the last 10 years and that despite all the valuable efforts to transparently report and display the potential risk of bias of primary studies, their impact on the overall findings of a systematic review is rarely formally assessed.

Reviewer: 2
This paper describes how assessments of risk of bias of RCTs included in systematic reviews are carried out and how such assessments are incorporated into the statistical analysis and overall findings.

Importance of work: There is considerable evidence that key information is often poorly reported in systematic reviews (SRs) (Moher 2007); that's why important agencies and international groups have produced guidelines and statements where the task of assessing the risk of bias of individual studies (as a component of assessing the strength of a body of evidence) is essential to improve the conduct and reporting of systematic reviews and meta-analyses. (Higgins 2008; CRD Guidance 2009; Viswanathan 2012; Moher 1999; Moher 2009) I think Authors correctly point out this important issue (assessments of risks of bias) in SRs reporting and how such assessments are included in overall findings. This paper is therefore of potential importance to a general readership, and particularly to systematic reviewers, in order to improve the suboptimal reporting of systematic reviews and meta-analyses.

Originality
The work is similar and findings consistent with those of Moja 2005 that evaluated SRs published between 1995 and 2002. The present research study underlines that in the last ten years no improvement has been observed in how systematic reviews incorporate the assessment risk of bias of primary studies into formal statistical analysis.

RESPONSE: We agree and as noted earlier have strengthened this is in our discussion and "What this study adds" section.

Scientific reliability
The aim of the study and outcome measures are clearly defined with appropriate reference to the literature. The overall study design is satisfactory. The study sample (Cochrane and non-Cochrane systematic reviews published between 1 January and 31 March 2012) is adequately described.

Methods
The planned study sample is clearly defined together with inclusion criteria; methods are adequately described in all aspects: study sample selection, data extraction and data analysis.

Results
Study findings are well presented. In Tables 1-2-3 are clearly described the outcome measures: characteristics of included SRs; method used for risk of bias assessment in primary studies; presentation and incorporation of risk of bias assessments into the analysis of individual systematic reviews.

Interpretation and conclusions
The study aims have been answered. The findings are consistent with other studies (Moher 2007; Jadad 1998). Results show better reporting in Cochrane reviews and specifically the fact that they were much more likely to assess individual methodological component as I expected. I agree with the Authors about the potential underestimation of the problem by extracting non-Cochrane reviews from DARE database compared to systematic reviews identified from other sources. Finally this work points out an important issue: both Cochrane and non-Cochrane reviews largely failed in how risk of bias assessment were incorporated into the statistical analysis and interpretation of the overall conclusions.